

Transitions from first substance use to substance use disorders in adolescence: Is early onset associated with a rapid escalation?

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Abstract

Background: Early substance use (SU) in adolescence is known to be associated with an elevated risk of developing substance use disorders (SUD); it remains unclear though whether early SU is associated with more rapid transitions to SUD.

Objective: To examine the risk and speed of transition from first SU (alcohol, nicotine, cannabis) to SUD as a function of age of first use.

Methods: N = 3021 community subjects aged 14–24 years at baseline were followed-up prospectively over 10-years. SU and SUD were assessed using the DSM-IV/M-CIDI.

Results: (1) The conditional probability of substance-specific SU-SUD transition was the greatest for nicotine (36.0%) and the least for cannabis (18.3% for abuse, 6.2% for dependence) with alcohol in between (25.3% for abuse; 11.2% for dependence). (2) In addition to confirming early SU as a risk factor for SUD we find: (3) higher age of onset of any SU to be associated with faster transitions to SUD, except for cannabis dependence. (4) Transitions from first cannabis use (CU) to cannabis use disorders (CUD) occurred faster than for alcohol and nicotine. (5) Use of other substances co-occurred with risk and speed of transitions to specific SUDs.

Conclusion: Type of substance and concurrent use of other drugs are of importance for the association between age of first use and the speed of transitions to substance use disorders. Given that further research will identify moderators and mediators affecting these differential associations, these findings may have important implications for designing early and targeted interventions to prevent disorder progression.

Keywords: Substance use disorder; Age; Initiation; Transition; Adolescence; Epidemiology

1. Introduction

Early onset of substance use (SU) is related to an elevated risk of substance use disorder (SUD) (Grant and Dawson, 1997; DeWit et al., 2000; Breslau et al., 1993; Chen et al., 2005). Available data though suggest that the relationship is complex and our knowledge about the speed of transition from first use to DSMIV abuse or dependence in adolescence and particularly of age at first use and its relation to the speed of transitions for different substances is still limited (Chen et al., 2005). This is likely due to methodological factors (e.g. differences in definitions of early onset) and a deficit of prospective-longitudinal studies on SUD incidence in adolescence (Rehm et al., 2005).

This paper investigates for various substances, whether early onset of SU is associated with a more rapid progression to SUD in adolescence and examines the role of concurrent other SU.

Such information can enhance understanding of SUD development in adolescence and may provide crucial data about time periods in which intervention may be promising.

There is little disagreement that early SU onset is associated with an increased risk of SUD. This has been shown for transitions from alcohol use to alcohol disorders (Nelson and Wittchen, 1998a; Brook et al., 2002; Grant and Dawson, 1997; DeWit et al., 2000), from nicotine use to nicotine dependence (Breslau et al., 1993), from cannabis use to cannabis dependence (Chen et al., 2005) and from any illicit SU to illicit SUD (Grant and Dawson, 1998). Animal research has shown tendencies for more intensive SU and for SU in response to distressing events in younger subjects (Siegmund et al., 2005; Füllgrabe et al., 2007; Adriani et al., 2002). While the role of physiological and social factors for the transition to SUD in adolescents with early SU is not clear yet, these subjects may be at risk of more rapid transitions to SUD. Chen et al. (2005) have shown that a younger age of first cannabis use (CU) was associated with an elevated risk of cannabis dependence within the first 24-months after first CU. This may suggest more rapid transitions in those with early CU onset. However, subjects with early onset of alcohol use also had a higher risk of transition to alcohol disorders, but made the transition more slowly (DeWit et al., 2000). Anthony and Petronis (1995) reported similar findings for transition to illicit substance use problems and showed that the elevated risk in early onset users was independent of the time between first use and disorder onset.

Differences between substances concerning the speed of transition from use to dependence, and from abuse to dependence, have been found in studies with subjects from the community (Wagner and Anthony, 2002) and from partially clinical samples (Ridenour et al., 2005). However, these studies do not exclusively cover adolescence and young adulthood and provide little information about transition from use to abuse and transitions to nicotine dependence. Differences between substances in speed of transition from use to dependence were evident in an adolescent sample consisting of largely males and offspring of parents with SUD (Ridenour et al., 2006). With this background and also with consideration of differences in drug policies between countries, it is pertinent to investigate these issues in a representative community sample from Germany.

This present study investigates the speed of transition from first SU to abuse, and from first SU to dependence, for alcohol, cannabis, and nicotine using 10-year prospective-longitudinal data from a representative community sample from Germany. We also investigate the relation between age of onset of SU and the risk and speed of transition to SUD, taking into account concurrent other SU. The aims of the present study were:

- (1) to examine the transition time from first use to SUD for nicotine, alcohol and cannabis in adolescence;
- (2) to assess whether early use in adolescence is associated with a higher risk of transition, and shorter transition time, to abuse or dependence;
- (3) to assess whether concurrent use of other substances is associated with the risk and speed of transition.

2. Methods

2.1. Sample and overall design

Data were collected as part of the EDSP study, a 10-year prospective-longitudinal community study on the course and risk-factors for SU and SUD of a stratified sample of N= 3021 subjects aged 14–24 years at baseline. Because the study emphasized early developmental stages of psychopathology, individuals aged 14–15 years were sampled at twice the probability of those aged 16–21 years. Individuals aged 22–24 years were sampled at half the probability of those aged 16–21 years. Detailed descriptions of the sample, the study design and objective have been reported elsewhere (Lieb et al., 2000; Wittchen et al., 1998a). The baseline sample was drawn from metropolitan Munich (German government registries) in 1994 and was followed-up over a 10-year period with up to three follow-up examinations. The baseline survey was conducted in 1995 (T0, N= 3021); the follow-up examinations were carried out approximately 1.6 years (T1, median interval since baseline, only for the younger cohort of N= 1228 subjects aged 14–17 years at baseline), 3.5 years (T2) and 8.2 years (T3) later. Response rates (proportions of the baseline sample) were 71% at T0 (N= 3021), 84.3% (N= 2548) at T2 and 73.2% (N= 2210) at T3. The retention rates (proportions of the sample of the preceding wave) were: 88.0% (T0–T1), 88.8% (T1–T2), and 79.4% (T2–T3) in the younger cohort and 84.8% (T0–T2) and 80.6% (T2–T3) in the older cohort. At T3, the age range was 21–34 years. We tested whether baseline alcohol, nicotine and cannabis use predicted attrition. In the younger cohort, CU at baseline was associated with dropout at T3 (OR 0.66, 95% CI: 0.4–0.9, $p = 0.015$). In the older cohort, baseline nicotine use was associated with drop-out at T3 (OR 0.71, 95% CI: 0.5–0.9, $p = 0.027$).

2.2. *Diagnostic assessment*

At each assessment wave, participants were assessed with the baseline or respective follow-up computer-assisted versions of the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI) (Wittchen et al., 1998b; Wittchen and Pfister, 1997), an updated version of the World Health Organisation (WHO) CIDI (Wittchen and Semmler, 1990). The M-CIDI is a fully standardized diagnostic interview designed for epidemiological research (Wittchen et al., 1998b) to assess symptoms, syndromes and diagnoses of 48 mental disorders along with information about onset and duration. The diagnoses presented in this article are based on the computerized M-CIDI/DSM-IV algorithms. The DIA-X/M-CIDI administration includes a respondent booklet that includes (e.g.) symptom and SU lists in order to help the participant in answering complicated symptom questions and dating age of onset. The test–retest reliability and validity of the DIA-X/M-CIDI diagnoses have been established (Reed et al., 1998; Wittchen et al., 1998b; Wittchen, 1994). Test–retest reliability was satisfactory for nicotine dependence (Kappa = 0.64), any drug disorder (Kappa = 0.64), and any alcohol disorder (Kappa = 0.78) (Wittchen et al., 1998b). Validity was established; for example for alcohol abuse (Kappa = 0.83) and for any drug disorder (Kappa = 0.64) (Lachner et al., 1998). The intra-class-coefficients were good for the age at which the first dependence criterion for nicotine dependence was met (ICC = 0.83) (Wittchen et al., 1998b), and for age at first use of nicotine (ICC = 0.83), alcohol (ICC = 0.96), and illicit substances (ICC = 1.00) (Lachner et al., 1998). All interviewers had received intensive 1-week training on the DIA-X/M-CIDI, followed by at least 10 closely monitored practice interviews at baseline and booster sessions before each subsequent wave.

2.2.1. *Assessment of SU and SUD.* SU and SUD were assessed with the three separate DIA-X/M-CIDI-sections for nicotine, alcohol, and medication and illicit substance use. Each section first establishes the quantity and frequency of SU along with age of onset and recency information. Diagnostic criteria are only assessed if criteria for minimal SU are met and, in the case of illicit substances, if participants are willing to answer these questions truthfully. Criteria for minimal SU were: (a) tobacco use at least once per day over a 1-month period; (b)

at least regular alcohol consumption (at least three times a week or more than three standard drinks per drinking day during the past 12 months in subjects who had drunk on more than 12 occasions in at least 1 year of their lives; applied for alcohol dependence); alcohol use on at least 13 occasions in a 12-month period (for alcohol abuse); (c) illicit SU more than four times. For alcohol dependence, we used two screening questions in order to include subjects, who did not meet the criterion described above but met the minimal use criteria in shorter periods. Participants were asked whether they would answer questions on illicit substances truthfully (commitment probe). Subjects who declined were excluded from analyses concerning illicit substances (87 subjects at T0, 17 subjects at T1, 20 subjects at T2, and 22 subjects at T3; 146 subjects in all).

The base rates for substances other than alcohol, nicotine, and cannabis were too low to allow for the statistical approaches used.

The following use levels were considered: no use, any use, DSM-IV abuse, and DSM-IV-dependence (abuse and dependence were non-hierarchical). In keeping with current nomenclature, DSM-IV abuse and dependence are analysed separately.

2.3. Statistical analysis

Data were weighted to account for different sampling probabilities at baseline according to age, and response rates at baseline varying over age, gender, and geographic region. The Stata Software package 9.2 (StataCorp., 2007) was used for all calculations and to compute robust variances, confidence intervals, and p-values (by applying the Huber–White sandwich matrix) required when basing analyses on weighted data (Royall, 1986). Cumulative lifetime incidence was generated using the LOCF (Last Observation Carried Forward) method, i.e. the information obtained until the last available assessment was taken into account. This allowed using information from subjects who dropped out of the study during the assessments. The Kaplan–Meier (Therneau and Grambsch, 2000) estimator was used to estimate the age-dependent cumulative lifetime incidence of SU and SUD. Hereby, age of onset information was aggregated from the assessments by using the minimum age of onset reported. When comparing this approach to the use of the age of onset reported first, intraclass correlations were very high for age of onset of alcohol use ($\rho = 0.99$), nicotine use ($\rho = 1.00$), cannabis use ($\rho = 1.00$), alcohol abuse ($\rho = 0.96$), alcohol dependence ($\rho = 0.96$), nicotine dependence ($\rho = 0.96$), cannabis abuse ($\rho = 0.96$), and cannabis dependence ($\rho = 0.99$).

Cox regressions were applied to assess overall differences in the risk of developing SUD over time between groups with different ages at onset of SU. We allowed for different curves according to age and gender (“stratified Cox regression”, Therneau and Grambsch, 2000). To assess whether group differences varied over time, the proportional hazard assumption was tested using Schoenfeld residuals (Therneau and Grambsch, 2000). When the assumption was violated, the interaction term covariate \times number of years since SU was added to the model in order to improve the model fit and to assess how strongly the hazard ratios depended on time. Here, the model-based time-dependent hazard ratio equals HR (main effect of covariate) \times HR (interaction effect of covariate)number of years. Again the proportional hazard assumption was tested using Schoenfeld residuals. If still a poor fit was found we determined time intervals between which the hazard ratios showed the highest differences in an exploratory way. We applied the model for each substance separately, i.e. for the transition from nicotine use to nicotine dependence. This was done to consider differences in the speed of transition to SUD between groups with different ages at onset of SU. In a second step of analysis, we adjusted the results for the presence of the use of other substances (alcohol, nicotine,

cannabis, other illicit substances) prior to the SUD of the substance under consideration. All subjects who had used the substance and provided age of onset information (see below) were included in the analyses on the risk and speed of transition.

Few subjects had not provided information on age of onset of SU and/or SUD. Data from these subjects could not be used in the discrete-time survival analyses. For analyses on risk and speed of the transition, complete age of onset information for SU and SUD was required. However, in some cases such information was missing (alcohol: N= 7 for abuse, N= 8 for dependence; nicotine: N= 10 for dependence; cannabis: N= 15 for abuse, N= 6 for dependence). In addition, a number of cases had reported onset of SUD as prior to onset of SU: 21 (2.9%) for alcohol abuse, 6 (1.9%) for alcohol dependence, 11 (1.3%) for nicotine dependence, 17 (5.7%) for cannabis abuse, and 6 (5.9%) for cannabis dependence (percentages refer to the total number of those who had the respective SUD and who had provided age of onset information for SU and SUD). These cases were therefore excluded from the Cox-regression analysis. It should be noted though that for incidence and prevalence rates as given in Section 3.1, no age of onset information was required and the subjects who had not provided this information were included in this part of the analysis.

For the test of group differences, we only considered groups with at least N= 10 individuals. The time scale used to assess transitions between SU and SUD was the number of years since the onset of SU. Since cases with SU and SUD onset within the same 12-months period (i.e. length of transition = 0 years) are otherwise automatically excluded from the Cox-regression analysis, we shifted the time scale 1 year upwards to include all cases in the Cox regression, replacing 0 years by 1 year, 1 year by 2 years, and so on. This approach was not used for the curves in Figs. 1 and 2.

A commonly used definition of early SU onset in adolescence is still lacking. A definition of early onset as onset in adolescence in comparison to adulthood may be problematic, since SU onset normally occurs in adolescence. As a result, we chose to use different definitions of age of onset in an exploratory way, taking into account each year of the high-risk phase for initial SU in adolescence as a threshold for early onset in adolescence in comparison to later onset. We defined the high-risk phase as the phase with the steepest increase in the survival curve for incident SU (see Section 3.2). For instance, for the high-risk phase for first alcohol use between age 10 and 16 years, we first defined early age of onset as \leq age 10 years and later age of onset as $>$ age 10 years; then we stepwise shifted the limit between early vs. later onset of use from age 10 to 16 years.

3. Results

3.1. Baseline lifetime prevalence and cumulative lifetime incidence

At baseline 94.5% reported any alcohol use, 76.3% any nicotine use and 33.9% any CU. At the end of the observation period, cumulative incidence rates for any SU were 97.7% for alcohol, 79.2% for nicotine, and 50.7% for cannabis. Baseline rates for SUD were 13.7% for alcohol abuse, 3.7% for cannabis abuse, 18.8% for nicotine dependence, 6.2% for alcohol dependence, and 1.5% for cannabis dependence. Cumulative incidences for SUD up to T3 were 24.7% for alcohol and 9.3% for cannabis abuse, 28.5% for nicotine dependence, 11.0% for alcohol dependence, and 3.1% for cannabis dependence (table including total numbers available upon request).

3.2. Age of onset

Survival analyses were conducted to describe age of onset distributions. In the following text, the steepest increase in the survival curve is described. First alcohol use mainly occurs between ages 10 and 16 years, first nicotine use between ages 11 and 17 years, and first CU between ages 14 and 19 years. The main onset interval was age 14–18 years for alcohol and age 15–20 years for cannabis abuse. For dependence, the main onset interval was age 14–19 years for nicotine, age 15–19 years for alcohol and age 15–18 years for cannabis (figures available upon request).

3.3. Proportion and time length of transitions to SUD

Up to T3, the conditional abuse rates were 25.3% (weighted percents) of alcohol users and 18.3% of cannabis users. Conditional dependence rates were 36.0% for nicotine, 11.2% for alcohol and 6.2% for cannabis.

Figs. 1 and 2 display the time lapses from first use to onset of abuse and from first use to onset of dependence for all subjects who developed the respective disorder. Cannabis abuse (N= 283) occurs earlier after first CU than alcohol abuse after first alcohol use (N= 713). Almost 30% of cases with cannabis abuse had occurred at 1 year after onset of CU, 50% at 2 years, and 70% at 3 years. In comparison, 10% of all alcohol abuse cases had occurred at 1 year after first alcohol use, 30% at 2 years, and 60% at 4 years. Only a few new cases of abuse occurred 10 years or more after onset of use of the respective substance. Transitions to cannabis dependence (N= 95) occurred more rapidly than transitions to nicotine dependence (N= 826) and to alcohol dependence (N= 313). 20% of all cases of cannabis dependence occurred during the first year after onset of CU, almost 60% had occurred at 2 years, and 70% at 3 years. In comparison, almost 20% of all cases of nicotine dependence had occurred at 1 year after first nicotine use, 40% at 2 years, and almost 70% at 4 years. For alcohol dependence, almost 30% of all cases had occurred until 2 years after first alcohol use, 40% at 3 years, and 50% at 4 years.

3.4. Risk and speed of transition by age at first use

We compared risk and speed of transition to SUD in late vs. early onset users using Cox regressions. The results are given in Table 1 (risk of transition) and Table 2 (speed of transition). Table 3 provides an explanatory summary of these results.

Early onset of alcohol use was associated with a higher risk but also with a lower speed of transition to alcohol abuse and dependence. For nicotine, early onset of use was related to an elevated risk of nicotine dependence but later onset of use was associated with a more rapid transition. Subjects with early CU onset had an elevated risk of transition to cannabis abuse and dependence. CU onset later in adolescence was associated with an elevated risk of a more rapid transition to cannabis abuse. For cannabis dependence, no interaction with time was found.

We also assessed the risk and speed of transition by exploring time periods with highest differences in hazard ratios; detailed information available upon request). With early onset defined as \leq age 14 years, later onset of use was associated with a higher risk of alcohol abuse during the first year after onset of alcohol use (HR 2.05, 95% CI: 1.4–2.9), but later onset users were less likely to develop the disorder in the following years (HR 0.52, 95% CI 0.4–0.6). With early onset defined as \leq age 13 years, later onset users were more likely to develop alcohol dependence during the first 2 years after onset of use (HR 2.31, 95% CI: 1.3–3.9).

Later onset of use was associated with a lower risk of the disorder in the following years (HR 0.48, 95% CI: 0.3–0.7). Differences were not significant after 12 years after onset of use. Regarding transitions to nicotine dependence (with early onset defined as \leq age 17 years), the difference in risk was not significant during the first year after onset of use (HR 1.43, 95% CI: 0.9–2.2). Thereafter, the risk of transition was lower for later onset users (HR 0.53, 95% CI: 0.3–0.8). From 8 years after onset of use, differences were not significant (HR 0.84, 95% CI: 0.2–3.0).

3.5. Concurrent use of other substances

As concurrent other SU may be associated with the risk and speed of transition to SUD we repeated the analysis adjusting for concurrent SU prior to the SUD under consideration (for a summary of the results see Table 3; detailed tables are available upon request).

We found that nicotine, cannabis and other illicit substance use co-occurred with the risk of transition to alcohol abuse in later onset users. Differences in risk between very early and later onset users now became significant (overall difference (age of onset \leq 10 years): HR 0.74, 95% CI: 0.5–0.9; overall difference (age of onset \leq 11 years): HR 0.69, 95% CI: 0.5–0.9; overall difference (age of onset \leq 12 years): HR 0.75, 95% CI: 0.6–0.9).

Also, nicotine, cannabis and other illicit substance use co-occurred with the risk and speed of transition to alcohol dependence in later onset users. Group differences in risk between early and later onset users were significant (overall difference (age of onset \leq 10 years): HR 0.61, 95% CI: 0.4–0.9; overall difference (age of onset \leq 11 years): HR 0.67, 95% CI: 0.4–0.9; overall difference (age of onset \leq 12 years): HR 0.68, 95% CI: 0.5–0.9; overall difference (age of onset \leq 13 years): HR 0.62, 95% CI: 0.4–0.8). In one step of the analyses, the hazard ratio for a more rapid transition in later onset users was not significant (interaction effect: HR main effect 0.98, HR interaction effect 0.89, 95% CI 0.80–1.00 (age of onset \leq 13 years)).

Alcohol, cannabis and other illicit substance use co-occurred with the risk of transition to nicotine dependence in later onset users (e.g. overall difference (age of onset \leq 11 years): HR 0.69, 95% CI: 0.5–0.9; overall difference (age of onset \leq 12 years): HR 0.65, 95% CI: 0.5–0.8; overall difference (age of onset \leq 13 years): HR 0.67, 95% CI: 0.5–0.8; overall difference (age of onset \leq 14 years): HR 0.71, 95% CI: 0.6–0.8).

For CUD, we found no changes in the results when controlling for alcohol, nicotine and other illicit substance use. For transitions to CUD, we repeated the analysis adjusting for alcohol abuse, alcohol dependence and nicotine dependence prior to onset of CUD. Also in this analysis there were no changes in results.

In exploring time periods with maximal differences in hazard ratios, we found the following results: with early onset of use defined as age \leq 14 years, later onset users were more likely to develop alcohol abuse during the first year after onset of alcohol use (HR 1.71, 95% CI: 1.1–2.5), but later onset users were less likely to develop the disorder in the following years (HR 0.49, 95% CI: 0.3–0.6). For transitions to alcohol dependence (early onset defined as \leq 13), no difference in risk during the first 2 years after onset of use was found (HR 1.58, 95% CI: 0.9–2.7). After this point, subjects with later onset of use were less likely to develop dependence (HR 0.42, 95% CI: 0.3–0.6). The difference in risk of transition to nicotine dependence (early onset defined as \leq 17) was not significant during the first year after onset of use (HR 1.03, 95% CI: 0.6–1.6). Thereafter, the risk of transition was lower for later onset users (HR 0.50, 95% CI: 0.3–0.8).

4. Discussion

Using data from a prospective-longitudinal community study, including the high-risk phase of SU and SUD in adolescence and early adulthood we described the transition times from first use (of alcohol, nicotine, and cannabis) to abuse of, and to dependence on these substances. In addition, we investigated the association between early SU onset and the risk and speed of transition to SUD. Each year of the high-risk phase of SU onset in adolescence was taken into account for a definition of early onset of use. The main findings are: (1) conditional SUD rates are highest for nicotine and lowest for cannabis. (2) The duration of transition from first SU to SUD is shortest for cannabis. (3) SU onset early in the high-incidence phase of SU in adolescence is associated with an elevated risk of SUD for all the substances. (4) SU onset later in adolescence is associated with a more rapid progression to SUD for alcohol abuse and dependence, nicotine dependence and cannabis abuse. (5) For subjects with later onset of SU, concurrent other SU is related to the increased risk of SUD (for alcohol and nicotine) and the increased speed of transition to alcohol dependence.

Our paper confirms adolescence as the core high-incidence phase for first SU and SUD as reported from earlier stages of our study (Lieb et al., 2000; Perkonig et al., 2006a, 1999; von Sydow et al., 2001; Nelson and Wittchen, 1998a,b) and other studies (Fergusson et al., 2006; Chen and Kandel, 1995; Boden et al., 2006; Costello and Erkanli, 1999; Monshouwer et al., 2005; Wagner and Anthony, 2002). We also confirm early SU onset as a risk factor for SUD. We extend these findings by examination of substance-specific differences in speed of transitions, the role of age in the speed of transitions, and the role of concurrent SU.

4.1. *Speed of transition from first SU to SUD*

We found that transitions to cannabis abuse and dependence occurred more rapidly than transitions to alcohol disorders and nicotine dependence. Thus far, this had only been observed for transitions to cannabis dependence in a study in which males and subjects with a parent with SUD were over-sampled (Ridenour et al., 2006). The similarity is interesting, since it occurred in spite of different sampling strategies and drug policies.

The finding of relatively rapid transitions to CUD seems inconsistent with the view that cannabis has little addictive potential (Nocon et al., 2006). However, conditional disorder rates were smallest for cannabis. This is surprising because the speed of transition and the proportion of transitions to cannabis dependence were consistent in a study with adolescents (Ridenour et al., 2006). This difference may be due to the different sampling strategies. As suggested by Ridenour et al. (2006), proportion and speed of transitions should be taken into account when measuring addictive liability. Our results raise the question why a small but considerable number of cannabis users made this fast transition. Factors that may account for this pattern will be discussed further below.

4.2. *Age of onset of SU*

Including the high-incidence phase of SU and SUD in adolescence, we show that SU early in adolescence is associated with an elevated risk of SUD for alcohol, nicotine and cannabis. The elevated risk occurred independent of time between first use and SUD as shown by Sung et al. (2004) and Anthony and Petronis (1995) for more general SU/SUD categories. Our findings suggest that differentiation between early and late onset in adolescence is a meaningful alternative to the differentiation between onset in adolescence and onset in

adulthood. SU onset later in adolescence was associated with a more rapid progression to SUD (with the exception of cannabis dependence). These findings suggest that an elevated risk of transition does not necessarily accompany an elevated speed of transition.

4.3. Transitions to alcohol disorders

Similar to DeWit et al. (2000), we found a higher risk and a lower speed of transition to alcohol disorders in those with early onset of alcohol use. Since risk and speed of transitions to alcohol dependence in later onset users co-occurred with other SU, transitions to alcohol use disorders in late adolescence may be influenced by other SU experiences.

The higher speed of transition in later onset users may also be due to the emergence of more intense drinking patterns (Reboussin et al., 2006), less alcohol related parental control (van Zundert et al., 2006) and greater opportunities to obtain alcohol in late adolescence. Interestingly, in animal studies examining the development of ethanol intake, a latency period of less ethanol consumption was observed in adolescent vs. adult rats after first ethanol use. After this period, the consumption of the younger rats reached the level of the adult animals (Siegmund et al., 2005). Early onset may contribute to vulnerability to factors occurring after onset of use. For example, rats with first ethanol consumption in adolescence as compared to adulthood showed a greater increase in ethanol consumption after stressful events (Siegmund et al., 2005; Füllgrabe et al., 2007). This may explain the combination of a greater risk and a slower transition in early onset users.

4.4. Transitions to nicotine dependence

Similar to Breslau et al. (1993), we found no difference in risk of transition to nicotine dependence for very early onset users in the unadjusted model. In our sample, the risk of transition of later onset users co-occurred with other SU. Adjustment for other SU revealed an elevated risk for nicotine dependence for those with very early onset. The elevated risk of a more rapid transition to nicotine dependence in later onset users may be explained by higher social acceptance and more opportunities of regular smoking in late adolescence. Later onset of smoking is associated with a faster transition to daily smoking (Breslau et al., 1993). This is somewhat in contrast to animal research that has shown greater nicotine self-administration in rats with onset of nicotine use in adolescence (Levin et al., 2003) and in mice in early vs. later adolescence (Adriani et al., 2002). On the other hand, mice in early adolescence show a distinct but delayed compensatory reaction when confronted with reduced nicotine concentration in a solution. Also, proximal behaviour outcomes of nicotine consumption differed in early vs. late adolescent mice (Adriani et al., 2002). Effects of nicotine are possibly experienced as more pleasant in late adolescence, which would explain the more rapid transitions in late adolescence. Also, nicotine withdrawal was more distinct in adult rats (O'Dell et al., 2006), a phenomenon that could be related to more rapid transitions later in human adolescence.

4.5. Transitions to CUD

We confirmed early onset of CU as a risk-factor for CUD, but early use was not associated with a more rapid transition to CUD. In a study of Chen et al. (2005) early onset of use was associated with an elevated risk of dependence within 24 month after first CU. This may be due to the risk of transition associated with early CU onset and the high speed of transitions to CUD. The age-risk association may be related to an increase in adverse effects of cannabis with age, a phenomenon that has been described in animal research (Schramm-Sapyta et al.,

2007). Also, those who developed CUD after early CU onset may be particularly vulnerable because of other factors as for example other mental disorders associated with CU and CUD (Wittchen et al., 2007).

4.6. Implications for interventions

Our findings have several implications for interventions. Early onset users are at an elevated risk of SUD, even if the transition may not be immediate. Careful attention should be paid to factors that may “trigger” transitions to SUD in early onset users. Interventions should take into account the speed of transitions to CUD, and the speed of transitions in later onset users. As a result, simply delaying first use may not be a sufficiently promising intervention for SUD. However, delaying first SU is important because early SU is a risk-factor for SUD. Primary prevention approaches addressing behaviour problems in first grade are associated with a decreased risk of nicotine, but not of alcohol, inhalant and cannabis use by age 14 years (Furr-Holden et al., 2004). Interventions should also address concomitant SU as it is related to the risk and speed of transitions. Given that at least one-time alcohol, nicotine and cannabis use is widespread in this sample, secondary prevention aimed at transitions to regular use is important. Of particular concern is that subjects with regular legal SU, but no SUD, had low service use rates (Perkonig et al., 2006b). Other strategies to reach this population before the transition to SUD are necessary.

4.7. Implications for future research

Other areas of future investigation include the relation of other factors to SU patterns, and other vulnerabilities and risk factors associated with the risk and speed of transitions. Future research should investigate whether early onset of SU is a general marker for problematic development, a moderator, or a mediator moderated by for example early developmental problems.

It is of interest to identify general and substance-specific factors that may be associated with risk in comparison to timing, i.e. speed of transition. Also, further differences between later and early onset users have to be identified. For example, family history (e.g. parental mental disorder) and mental disorders in adolescence are associated with CU initiation and progression (von Sydow et al., 2002; Höfler et al., 1999; Wittchen et al., 2007); but their association with the speed of transition remains to be investigated in representative samples. Early and late onset users may differ with regard to associated mental disorders, family genetic factors and personality traits (Sung et al., 2004; Obot et al., 2001; Costello and Erkanli, 1999; Elkins et al., 2006). Parental SU may function as a role model for adolescent SU (Alati et al., 2005; van Zundert et al., 2006) and thus influence the risk and speed of transitions. Most incident cases of SUD occur during a period with important developmental tasks, for example finishing school. Experience of low control in the work place in adolescence is prospectively associated with substance dependence (Reed et al., 2006) and may be associated with the higher speed of transitions in late adolescence.

Here, we investigated substance-specific transitions (e.g. from nicotine use to nicotine dependence), but in future research, it would be interesting to investigate whether early use of one substance is associated with the development of SUD related to another substance. Also, in keeping with current nomenclature, we analysed DSM-IV abuse and dependence separately. However, there is evidence that DSM-IV abuse and dependence may not be separable constructs (Saha et al., 2006). In future research, the two categories could be collapsed into one. With regard to our results on the incidence periods of SU and SUD and the

speed of transitions, frequency and duration of exposure alone are probably not a sufficient explanation. Other factors as social and cognitive affective developmental stages and periods of genetically determined increased vulnerability may be additional explanations. However, our study was not designed to address these important issues in sufficient detail.

4.8. Limitations

The age range of the sample restricted this analysis. SUD may occur later in life. Yet, results from this sample aged 21–34 years at the final wave suggest that SU and SUD incidence rarely occurs after age 20 years. This analysis did not investigate the role of other mental disorders and of different SU patterns, but this will be addressed in future analyses. The time difference between assessment waves is fairly large. We used retrospective age of onset information between waves, which may be subject to recall bias. In spite of high retention rates in general, baseline CU and nicotine use were associated with drop-out at T3. It cannot be ruled out that some especially severe cases were not considered in the analysis. The sample is from metropolitan Munich, a relatively wealthy German region with relatively liberal legislation on alcohol and nicotine use, but strictly enforced legislation on illegal drug use. These factors may have affected the observed SU behaviour in a complex way. Thus, results may not be generalizable to other populations with greater variation in SES and ethnicity. In this regard it is of importance that overall, onset of SU did not occur earlier in our sample than in US samples (Vega et al., 2002; Chen et al., 2005; Everett et al., 1999), with the exception that onset of alcohol use occurred later in the NESARC (Hingson et al., 2006). This difference may be due to cohort effects and different study designs. Finally it remains open whether associations between SU onset and the speed of transitions can also be confirmed on the level of SUD symptoms. The function of DSM-IV criteria may vary with age (Saha et al., 2006), and certain first symptoms may be especially prevalent in adolescents (Holly et al., 1997), even after minimal SU (Chen and Anthony, 2003).



Fig. 1. Duration of transition from first SU to abuse.

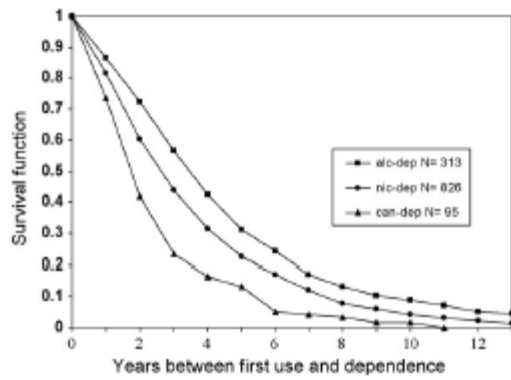


Fig. 2. Duration of transition from first SU to dependence.

Table 1
Associations between age at first SU and the risk of transition to SUD: overall difference

	Age at first use	N	Cum. % ^a	SUD	N	Hazard ratio	95% CI	Prob. >chi ^{2b}
Alcohol use (N= 2921)	≤10	290	9.70	Alcohol abuse (N= 713)	78	1.07	0.8–1.3	0.00
	≤11	412	13.20		120	0.96	0.7–1.2	0.00
	≤12	745	23.70		213	0.94	0.7–1.1	0.00
	≤13	1181	37.20		344	0.80	0.6–0.9	0.00
	≤14	1831	59.40		518	0.71	0.5–0.8	0.00
	≤15	2329	77.80		635	0.61	0.4–0.8	0.02
	≤16	2683	91.90		693	0.49	0.3–0.7	0.08
Alcohol use (N= 2921)	≤10	290	9.70	Alcohol dependence (N= 313)	37	1.13	0.7–1.7	0.00
	≤11	412	13.20		50	1.15	0.8–1.6	0.00
	≤12	745	23.70		94	1.00	0.7–1.3	0.00
	≤13	1181	37.20		154	0.77	0.6–1.0	0.00
	≤14	1831	59.40		228	0.73	0.5–1.0	0.01
	≤15	2329	77.80		283	0.56	0.3–0.8	0.36
Nicotine use (N= 2294)	≤11	220	8.60	Nicotine dependence (N= 826)	82	1.24	0.9–1.5	0.00
	≤12	473	18.10		203	0.97	0.8–1.1	0.00
	≤13	829	30.80		353	0.88	0.7–1.0	0.00
	≤14	1272	49.40		515	0.86	0.7–1.0	0.00
	≤15	1660	68.10		659	0.79	0.6–0.9	0.00
	≤16	1940	82.10		745	0.71	0.5–0.9	0.00
	≤17	2091	89.50		781	0.77	0.5–1.1	0.01
	≤18	2171	93.50		802	0.68	0.4–1.1	0.00
Cannabis use (N= 1343)	≤14	130	7.40	Cannabis abuse (N= 283)	54	0.48	0.3–0.7	0.89
	≤15	323	18.50		113	0.50	0.3–0.7	0.99
	≤16	575	35.40		180	0.45	0.3–0.6	0.93
	≤17	815	52.40		237	0.33	0.2–0.5	0.60
	≤18	1017	68.50		265	0.29	0.1–0.5	0.01
	≤19	1120	77.30		272	0.29	0.1–0.6	0.14
Cannabis use (N= 1343)	≤14	130	7.40	Cannabis dependence (N= 95)	24	0.31	0.1–0.5	0.91
	≤15	323	18.50		47	0.31	0.1–0.5	0.93
	≤16	575	35.40		65	0.34	0.2–0.6	0.90

All results concerning users with later onset in comparison to users with early onset of use.

^a Percents weighted.

^b Prob. chi² <0.05 indicates an interaction with time.

Table 2

Age at onset of SU and the speed of transition to SUD: model of interaction with time

	Age at first use	N	Cum. % ^a	SUD	N	Main effect ^b , Hazard ratio	95% CI	Interaction effect ^b , Hazard ratio	95% CI
Alcohol use (N=2921)	≤10	290	9.70	Alcohol abuse (N=713)	78	6.07	3.4–10.6	0.72	0.66–0.79
	≤11	412	13.20		120	3.81	2.4–6.0	0.76	0.70–0.82
	≤12	745	23.70		213	2.90	2.0–4.1	0.78	0.72–0.84
	≤13	1181	37.20		344	1.80	1.3–2.4	0.82	0.76–0.88
	≤14	1831	59.40		518	1.33	0.9–1.8	0.85	0.78–0.92
	≤15	2329	77.80		635	0.74	0.4–1.2	0.95	0.85–1.06
	≤16	2683	91.90		693	0.64	0.2–1.7	0.93	0.72–1.19
Alcohol use (N=2921)	≤10	290	9.70	Alcohol dependence (N=313)	37	4.59	2.0–10.2	0.77	0.66–0.88
	≤11	412	13.20		50	3.59	1.8–7.0	0.80	0.70–0.90
	≤12	745	23.70		94	2.20	1.2–3.8	0.84	0.75–0.93
	≤13	1181	37.20		154	1.43	0.8–2.4	0.86	0.76–0.97
	≤14	1831	59.40		228	1.12	0.6–2.0	0.89	0.77–1.02
	≤15	2329	77.80		283	0.71	0.3–1.4	0.93	0.79–1.10
Nicotine use (N=2294)	≤11	220	8.60	Nicotine dependence (N=826)	82	4.98	2.8–8.6	0.74	0.66–0.83
	≤12	473	18.10		203	2.29	1.5–3.3	0.80	0.73–0.87
	≤13	829	30.80		353	1.64	1.2–2.2	0.83	0.77–0.90
	≤14	1272	49.40		515	1.50	1.1–2.0	0.84	0.77–0.91
	≤15	1660	68.10		659	1.41	1.0–1.9	0.82	0.75–0.90
	≤16	1940	82.10		745	1.26	0.8–1.9	0.81	0.71–0.93
	≤17	2091	89.50		781	1.47	0.8–2.5	0.78	0.64–0.95
	≤18	2171	93.50		802	1.73	0.8–3.5	0.66	0.47–0.93
Cannabis use (N=1343)	≤14	130	7.40	Cannabis abuse (N=283)	54	0.49	0.3–0.7	0.99	0.89–1.10
	≤15	323	18.50		113	0.49	0.3–0.7	1.01	0.90–1.13
	≤16	575	35.40		180	0.40	0.2–0.6	1.04	0.94–1.16
	≤17	815	52.40		237	0.27	0.1–0.4	1.07	0.94–1.21
	≤18	1017	68.50		265	0.14	0.0–0.3	1.26	1.07–1.48
	≤19	1120	77.30		272	0.14	0.0–0.4	1.29	1.03–1.62
Cannabis use (N=1343)	≤14	130	7.40	Cannabis dependence (N=95)	24	0.33	0.1–0.6	0.96	0.78–1.19
	≤15	323	18.50		47	0.32	0.1–0.7	0.97	0.77–1.23
	≤16	575	35.40		65	0.31	0.1–0.6	1.03	0.82–1.29

All results concerning users with later onset in comparison to users with earlier onset of use.

^a Percents weighted.

^b Interaction with time: (a) HR (main effect) >1 and HR (interaction effect) <1: SUD occurs earlier in later onset users (under the condition that SUD occurs). (b) HR (main effect) <1 and HR (interaction effect) <1: SUD occurs later in later onset users (under the condition that SUD occurs). (c) HR (main effect) <1 and HR (interaction effect) >1: SUD occurs earlier in later onset users (under the condition that SUD occurs). (d) HR (main effect) >1 and HR (interaction effect) >1: SUD occurs later in later onset users (under the condition that SUD occurs).

Table 3

Age at onset of SU and the risk and speed of transition to SUD: explanatory summary of Tables 1 and 2

SUD	Age at first use	Difference in risk	Difference in speed	Difference in risk (controlled for other SU)	Difference in speed (controlled for other SU)
Alcohol abuse	≤10	ns	+	—	+
	≤11	ns	+	—	+
	≤12	ns	+	—	+
	≤13	—	+	—	+
	≤14	—	+	—	+
	≤15	—	ns	—	ns
	≤16	—	ns	—	ns
Alcohol dependence	≤10	ns	+	—	+
	≤11	ns	+	—	+
	≤12	ns	+	—	+
	≤13	ns	+	—	ns
	≤14	—	ns	—	ns
	≤15	—	ns	—	ns
Nicotine dependence	≤11	ns	+	—	+
	≤12	ns	+	—	+
	≤13	ns	+	—	+
	≤14	ns	+	—	+
	≤15	—	+	—	+
	≤16	—	+	—	—
	≤17	ns	+	—	+
	≤18	ns	+	—	+
Cannabis abuse	≤14	—	ns	—	ns
	≤15	—	ns	—	ns
	≤16	—	ns	—	ns
	≤17	—	ns	—	ns
	≤18	—	+	—	+
	≤19	—	+	—	+
Cannabis dependence	≤14	—	ns	—	ns
	≤15	—	ns	—	ns
	≤16	—	ns	—	ns

(+/—) Indicate a higher/lower risk or speed in later onset users compared to earlier onset users; ns indicates non-significant.

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The EDSP project and its family genetic supplement has been approved by the Ethics Committee of the Medical Faculty of the Technische Universität Dresden (No.: EK-13811). All participants provided informed consent.

Contributors

Silke Behrendt planned the analysis and wrote the manuscript.

Dr. Beesdo, Dr. Wittchen, Dr. Lieb and Dr. Höfler provided supervision of and substantial contribution to the writing of the manuscript.

Dr. Höfler also provided supervision and substantial contribution to the planning and conduction of the statistical analysis. All authors contributed to and have approved of the final version of the manuscript.

Conflict of interest

Silke Behrendt and Dr. Höfler state that they do not have a conflict of interest.

Dr. Beesdo has a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation. She receives or has in the past 3 years received Speaking Honoraria from: Pfizer.

Dr. Wittchen has a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation. He receives or has in the past 3 years received Research Support from: Eli Lilly and Company; Novartis; Pfizer; Schering-Plough.

He is currently or has been in the past three years a consultant for: Eli Lilly; GlaxoSmithKline Pharmaceuticals; Hoffmann-La Roche Pharmaceuticals; Novartis; Pfizer; Wyeth.

He receives or has in the past 3 years received Speaking Honoraria from: Novartis; Schering-Plough; Pfizer; Wyeth.

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